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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Addendum to the Advisory.

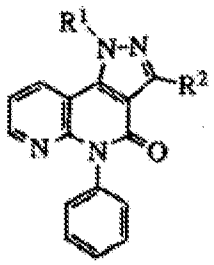
Applicants have amended the claims to 2 compounds.

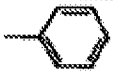
The rejection under 35 USC 103 EP 0526840 and US 5281610 still stands.

Applicants declaration has data for one compound. However this difference in activity is not considered to be unexpected.

The EP reference teaches several compounds in table 1, page 10

Table 1



Compound No	$-R^1$	$-R^2$
1	$-H$	
2	$-H$	$-CH_3$
3	$-H$	$-CH_2CH(CH_3)_2$

The inhibition and activity rate for these are given as

Table 2

Compound No.	Inhibition rate (%)	
	10^{-6}M	10^{-5}M
1	77.2	85.8
2	85.8	92.4
3	77.2	74.9

It can be seen that the variation is considerable.

At the time of the invention, see EP 1236725 (in 1449), it was known that inhibition of PDE activity varies and this range of variation is not considered to be unexpected.

Further, for a comparison with compounds as disclosed in JP, A, 63-159382 (1988), the PDE-inhibiting activity was also measured for Compounds A and D in Table 1 of JP, A, 63-159382 (1988).

Table 1

Test Compounds	Inhibition of PDE Isoenzymes (IC_{50} : μM)				
	I	II	III	IV	V
Example No.2	>100	>100	>100	0.11	16
Example No. 3	>100	>100	>100	1.2	3.9
Example No. 5	22	>100	60	0.06	13
Example No. 6	>100	>100	>100	0.16	15
Example No. 7	>100	>100	>100	1.3	4.7
Example No. 8	>100	>100	>100	0.44	>100
Example No. 10	>100	52	24	1.5	13
Example No. 13	62	60	94	1.2	13
Example No. 14	83	85	59	1.5	5.1
Example No. 15	100	47	49	1.4	8.7
Example No. 16	98	63	69	1.9	7.4
Example No. 17	>100	>100	>100	2.2	>100
Example No. 23	>100	>100	>100	1.2	>100
Rolipram	>100	>100	>100	0.78-3.2	>100

[0014] Representative examples of compounds of the invention include the following:

1-(3-Nitrophenyl)-3-(pyridin-2-ylmethyl)-1,8-naphthyridin-2(1H)-one,
1-(3-Nitrophenyl)-3-(pyridin-3-ylmethyl)-1,8-naphthyridin-2(1H)-one,
1-(3-Cyanophenyl)-3-(pyridin-4-ylmethyl)-1,8-naphthyridin-2(1H)-one,
1-(3-Nitrophenyl)-3-(pyridin-4-ylmethyl)-1,8-naphthyridin-2(1H)-one,
1-(3-Nitrophenyl)-3-[2-(pyridin-2-yl)ethyl]-1,8-naphthyridin-2(1H)-one,
1-(3-Nitrophenyl)-3-[2-(pyridin-3-yl)ethyl]-1,8-naphthyridin-2(1H)-one,
1-(3-Nitrophenyl)-3-[2-(pyridin-4-yl)ethyl]-1,8-naphthyridin-2(1H)-one,
1-(3-Nitrophenyl)-3-[3-(pyridin-2-yl)propyl]-1,8-naphthyridin-2(1H)-one,
1-(3-Nitrophenyl)-3-[3-(pyridin-3-yl)propyl]-1,8-naphthyridin-2(1H)-one,
1-(3-Nitrophenyl)-3-[3-(pyridin-4-yl)propyl]-1,8-naphthyridin-2(1H)-one,
1-(3-Nitrophenyl)-3-[3-(1-oxypyridin-4-yl)propyl]-1,8-naphthyridin-2(1H)-one,
1-(3-Cyanophenyl)-3-[3-(pyridin-4-yl)propyl]-1,8-naphthyridin-2(1H)-one,

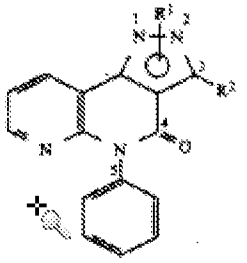
Some of the compounds differ only in the alkyl chain. And the activity changes. Thus variation in the activity is expected.

Applicants activity difference is not unexpected.

The rejection still stands.

The rejection of claims 1-24 (now 1-6, 8-15, 19-24) under 35 USC 103 over EP 0526840 and US 5281610 however still stands. Applicants declaration does have some data for one compound. Just the phenyl.

The prior art also has thienyl group and an alkyl chain . see below.



wherein R^1 is represents hydrogen, lower alkyl, aralkyl, or substituted or unsubstituted aryl, R^2 represents hydrogen, lower alkyl, thienyl, substituted or unsubstituted aryl, hydroxy or amino, or a pharmaceutically acceptable salt thereof.

The compound possesses antiinflammatory effect, immunosuppressive effect, broncho-dilatory effect and hair growth-stimulative effect.

The reference also teaches that they have bronco dilatory effect. Applicants claims are also drawn to the same treatment, "bronchial asthma" . Applicants argument that the A group with the linkage is a distinct feature for the acquisition of PDE IV inhibitory activity is not understood. The prior art compounds have the same activity as bronco dilators.

Applicants claims are also drawn to treating asthma and such which are also treated by bronchodilators.

Applicants arguments with respect to the advantages is also not convincing. The Sazuki reference may be just silent as to the type of inhibition, but it does treat the same disorder, Broncodilation, which is what is required to treat a number of bronchial disorders.

Applicants further argue that it has an unexpected increase in PDE IV inhibition

Applicants declaration does not compare all the closest art compounds and is not convincing.

WO 01/42244 and EP 1236 725, Aotsuka et al discloses the A group on a similar naphthyridin -2(1H)-one derivative. These are PDE IV inhibitors too.

These references have a methylene group with the A substitutent. (these references were provided in the IDS and are used only to overcome applicants arguments that the novelty of the activity is due to the CH2-A group)

Thus motivation to modify the US '610 compounds can also come from the teaching of WO '244 and '725 which have the substitutent similar to the one at the 3 position.

Thus the rejection still stands.

Conclusion

The rejection on claim 1 and 5 still stand.

Claims 1 and 5 are pending.

Claims 2-4, 6-24 have been cancelled.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rita J. Desai whose telephone number is 571-272-0684. The examiner can normally be reached on Monday - Friday, flex time..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Rita J. Desai
Primary Examiner
Art Unit 1625

R.D.
June 30, 2008

/Rita J. Desai/
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